Prothrombin Time as a Mirror of Immunological Capability in Polytrauma Patients, An IBM Watson Trauma Pathway Explorer© Analysis and Statistical Proof of Sepsis

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Prothrombin Time as a Mirror of Immunological Capability in Polytrauma Patients, An IBM Watson Trauma Pathway Explorer© Analysis and Statistical Proof of Sepsis

Philipp Vetter[1], Nikolas Wolf[2], Jan Hambrecht[1], Cédric Niggli[1], Jindrich Vomela[3], Hans-Christoph Pape[1], Ladislav Mica[1*]

Abstract

Triaging plays a pivotal role in the trauma bay after admission of polytrauma patients. The Watson Trauma Pathway Explorer® is an outcome prediction tool for Systemic Inflammatory Response Syndrome and sepsis within 21 days and death within 72 h in those patients. We aimed to analyze the time-related value of prothrombin time (PT) as sign of coagulopathy for sepsis. Retrospective data of 3653 patients were analyzed. According to sepsis development, two groups were formed. PT was generally measured until up to 48 h after admission to our trauma bay. Group differences were tested, and PT was analyzed as an independent predictor for sepsis, corrected for injury severity. Time-related threshold between groups were defined. Significant differences ($p < 0.05$) in PT between groups existed from admission over an hour and from 24 h to 48 h after admission. PT reached a minimum at 2 h after admission (60%) and normalized thereafter. The PT represented an independent predictor of sepsis at 24 h (PT: 86%; $p = 0.002$) and 48 h (PT: 91%; $p < 0.001$) after admission. A PT of ≤ 50% was predictive at admission ($p < 0.001$) and tended to be predictive at 4 h after admission ($p = 0.068$). A PT of ≤ 25% was predictive at admission ($p = 0.011$). Threshold values reached a minimum at 2 h after admission (PT: 57%), normalizing thereafter. The results highlight the time-related role of PT for sepsis in polytrauma patients. Thereby re-assessment is enabled, and early appropriate measures are facilitated.

Keywords: Watson Trauma Pathway Explorer; Polytrauma; Sepsis

Introduction

Triaging plays a pivotal role in the trauma bay after admission of polytrauma patients. Clinical examination is complemented by evaluation of laboratory parameters to accurately estimate injury severity and probability for subsequent adverse events (AE), which can range from a systemic Inflammatory Response Syndrome (SIRS) to sepsis and to death [1-8]. Septic AE represent the most common cause of late death after trauma [9] and can be promoted by an immunological decompensation in the trauma context [10,11]. Forecasting such septic complications with early treatment decisions improves outcomes and minimizes complications [12]. The Watson Trauma Pathway Explorer® is an outcome prediction tool to predict SIRS and sepsis within 21 days as well as death within 72h, based on an internal data base of more than 3500 patients with continuing admission [5-8,13]. The tool offers the advantage of comparing individual patient parameters to a group reference at fixed time points up until 21 days after admission, enabling a constant re-evaluation. Coagulopathy is commonly present in polytrauma

Affiliation:

[1]Department of Trauma Surgery, University Hospital Zurich, 8091 Zurich, Switzerland.

[2]University of Zurich, 8050 Zurich, Switzerland.

[3]Division of Medical Sciences in Sportsmedicine, Faculty of Sports Studies, Masaryks University, 62500 Brno, Czech Republic.

***Corresponding author:**
Prof. Dr. Med. Ladislav Mica, PhD, FEBS, FACS, University Hospital Zurich Raemistrasse 100, 8091 Zurich, Switzerland.

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patients admitted to the trauma bay [14-21] and is associated with AE (SIRS, multi organ failure, sepsis, death) [18-21]. More specifically, a reduced prothrombin time (PT) was identified as a risk factor for sepsis in polytrauma patients, which is, in turn, linked to increased mortality [21]. The correlation between PT and mortality is confounded by injury severity [20,22-24] and pharmaceutical treatment [25,26], which causes heterogeneity in cutoff-values and thereby complicates clinical decision making [27,28]. Regarding the timely aspect, the significance of PT at admission is well researched [21-23,29,30], while information on its relevance over the further course is scarce, and again referenced to injury severity [20]. The aim of our study was to analyze the predictive value of PT for sepsis in a time-related manner while considering injury severity.

Methods

For analysis in the Watson Trauma Pathway Explorer®, we included retrospective data from our internal data base of 3653 (1996-2022) with continuing admission. Inclusion criteria were patients aged ≥ 16 years with an Injury Severity Score (ISS) ≥ 16 [31] that provided complete datasets. Patient that died prior to admission or were referred from external hospitals were excluded. According to the development of sepsis within the observational period of 21 days, two groups were formed. In all patients, PT was measured at previously defined time points (admission, 1, 2, 3, 4, 6, 8, 12, 24, and 48 h) after admission to our trauma bay at the University Hospital Zurich [5,7,8].

Definition of sepsis

According to the most extreme values in leucocyte count, respiratory rate, heart rate and temperature, the SIRS score was calculated each day [32] over the time frame of hospitalization. Sepsis was defined as a SIRS score ≥ 2 with a focus of infection [33], and had to occur within 21 days, representing the observational period. Despite the existence of newer definitions, the above used definition showed a higher predictive ability [19].

Laboratory analysis

PT by means of percentage activity [%] was measured at the Institut für Klinische Chemie at the University of Zurich in a standardized blood gas analyzer (Radiometer ABL 825 Flex, Radiometer RSCH GmbH, Thalwil, Switzerland). The same procedure of measurement was applied at each time point.

Statistical analysis

Patients' baseline characteristics are described as means with standard deviations (SD) for numerical variables, as medians with interquartile ranges (IQR) for ordinal data and as percentages for binary variables. To assess differences between groups, an unpaired t-test for numerical variables and a Mood's median test for ordinal variables were used.

For analyzing differences between groups according to the development of sepsis, the Mann-Whitney-U-Test was used after noting a missing normal distribution according to a Q-Q-plot and an unequal variance. PT is described as median with IQR. It was tested as an independent predictor for sepsis by performing a binary logistic regression. This regression was also performed with PT cut-off values of ≤50% and ≤25%. Binary logistic regression was corrected for the confounding aspect of injury severity represented by ISS, New ISS (NISS) and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score [20]. Threshold values between the two groups according to sepsis development at each timepoint were calculated by the closest top-left threshold method. In a receiver operating characteristic, the calculated point is closest to the top-left corner and thereby indicates the maximum amount of combined sensitivity and specificity. SPSS 29.0 (IBM SPSS Statistics 29) served for data analysis. The level of significance was set a $p < 0.05$.

Ethical approval

The study was conducted according to the guidelines for good clinical practice and the Helsinki guidelines. The research was based on the TRIPOD statement, which represents a guideline for multivariable prediction model [34]. Ethical approval for analysis of patient data was granted by the ethical committee of the University Hospital Zurich and the government of Zurich upon the development of the database (Nr. StV: 1-2008) and reapproved for development of the Watson Trauma Pathway Explorer® (BASEC 2021-00391).

Results

Patient sample

The overall patient sample comprised 3653 cases with a mean age of 45.8 ± 20.2 years, with 73.4% being male (Table 1). Septic cases displayed higher values for the ISS, NISS and APACHE-II-Score, along with a younger age.

Group differences in prothrombin time according to the development of sepsis

Significant differences in PT existed from admission over an hour as well as 24 h until 48 h after admission (Figure 1). Generally, PT reached a minimum at 2 h after admission (60%) and normalized thereafter. Depending on the time point, a percentage of total patient sample values was missing: 673 (18.9%) at admission; 3095 (84.7%) at 1 h; 3399 (95.4%) at 2 h; 3247 (88.9%) at 3 h; 3133 (85.7%) at 4 h; 3066 (83.9%) at 6 h; 3122 (85.4%) at 8 h; 2663 (72.9%) at 12 h; 1827 (50.0%) at 24 h; 2186 (59.8%) at 48 h.

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Table 1: Baseline characteristics of the overall patient sample and groups according to development of sepsis. Prothrombin values are shown from admission onwards. Age [years], BMI [kg/m^2], temperature [°C], Systolic blood pressure [mmHg], Hemoglobin [g/dL], CRP [mg/L], PCT [ng/mL], Lactate [mmol/L], Prothrombin time [%].

Baseline characteristic	Overall patient sample N = 3653	Patients with developed Sepsis N = 547	Patients without developed sepsis N = 3106	p-value
Age (mean, SD)	45.8 ± 20.2	42.8 ± 18.1	46.3 ± 20.5	0.0002
Male	73.4%; N=2681	78.6%; N=430	72.4%; N=2251	-
Early death within 72h	19.3%; N=708	1.46%; N=8	22.5%; N=700	-
Blunt trauma	91.3%; N=3336	94.7%; N=518	90.7%; N=2818	-
Head injury	38.3%; N=1400	44.8%; N=245	37.2%; N=1155	-
BMI at admission (mean, SD)	25 ± 4.4	25.9 ± 4.4	24.8 ± 4.3	<0.001
ISS (median, IQR)	25 (17–34)	30 (25–41)	25 (17–34)	<0.001
NISS (median, IQR)	34 (25–50)	41 (33–50)	34 (24–48)	<0.001
APACHE II at admission (median, IQR)	14 (7–21)	17 (11–21)	13 (6–21)	<0.001
GCS at admission (median, IQR)	10 (3–15)	3 (3–14)	11 (3–15)	<0.001
Temperature at admission (mean ± SD)	35.5 ± 1.7	35.4 ± 1.7	35.6 ± 1.7	0.131
Systolic blood pressure at admission (mean ± SD)	130.7 ± 27.6	128.5 ± 27.7	131.2 ± 27.5	0.0715
Hemoglobin at admission (mean ± SD)	11.4 ± 4	11 ± 2.8	11.5 ± 4.2	0.005
CRP at admission (mean ± SD)	13.74 ± 41.21	23.15 ± 62.96	11.94 ± 35.32	< 0.001
pH at admission (mean ± SD)	7.31 ± 0.13	7.30 ± 0.15	7.32 ± 0.13	0.00632
PCT at admission (mean ± SD)	1.23 ± 4.3	0.48 ± 0.56	1.15 ± 4.86	0.559
Lactate at admission (mean ± SD)	2.94 ± 2.53	2.94 ± 2.27	2.94 ± 2.58	0.943
Prothrombin time at admission (median, IQR)	84 (65-97)	80 (61-92)	85 (66-98)	0.010
Prothrombin time at 1 h (median, IQR)	81 (57-95)	67 (48-87)	84 (62-95)	< 0.001
Prothrombin time at 2 h (median, IQR)	57 (41-78)	56 (42-71)	57 (41-81)	0.721
Prothrombin time at 3 h (median, IQR)	66 (50-85)	61 (47-79)	67 (50-86)	0.125
Prothrombin time at 4 h (median, IQR)	75 (56-89)	73 (58-86)	75 (55-89)	0.158
Prothrombin time at 6 h (median, IQR)	78 (63-90)	79 (64-87)	78 (63-92)	0.378
Prothrombin time at 8 h (median, IQR)	80 (66-92)	79 (63-87)	81 (67-92)	0.184
Prothrombin time at 12 h (median, IQR)	87 (76-98)	84 (73-96)	88 (77-99)	0.073
Prothrombin time at 24 h (median, IQR)	89 (76-100)	84 (71-97)	91 (78-100)	< 0.001
Prothrombin time at 48 h (median, IQR)	96 (82-100)	87 (73-100)	98 (85-100)	< 0.001

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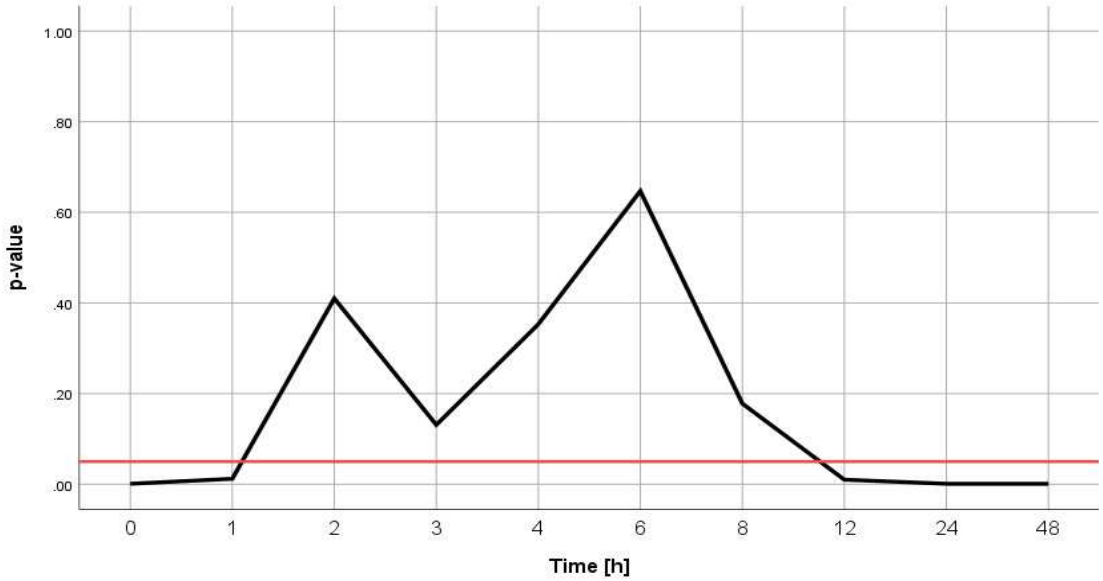

Figure 1: Group differences in prothrombin time according to the development of sepsis.

Prothrombin time as an independent predictor for sepsis, corrected for injury severity

The PT represented an independent predictor of sepsis at 24 h (PT: 86%; $p = 0.002$) and 48 h (PT: 91%; $p < 0.001$) after admission (Figure 2). A PT of ≤ 50% was predictive at admission ($p < 0.001$) and tended to be predictive at 4 h after admission ($p = 0.068$). A PT of ≤ 25% was predictive at admission ($p = 0.011$). Prediction analysis was corrected for ISS, NISS and APACHE-II-score since there was a respective correlation with PT at admission (ISS: $r = -0.311$; $p < 0.001$; NISS: $r = -0.275$; $p < 0.001$; APACHE-II-score: $r = -0.386$; $p < 0.001$).

Time-related threshold values in prothrombin time between groups according to sepsis development

Threshold values were defined at each timepoint. Similar to the value of the total patient sample, PT reached a minimum at 2 h (57%) after admission and normalized thereafter (Figure 3).

Discussion

Following up on previous reports [5,7,8] for the Watson Trauma Pathway Explorer®, a time-related analysis of PT regarding its association with sepsis in polytrauma patient was performed. PT showed a relation to sepsis in the early

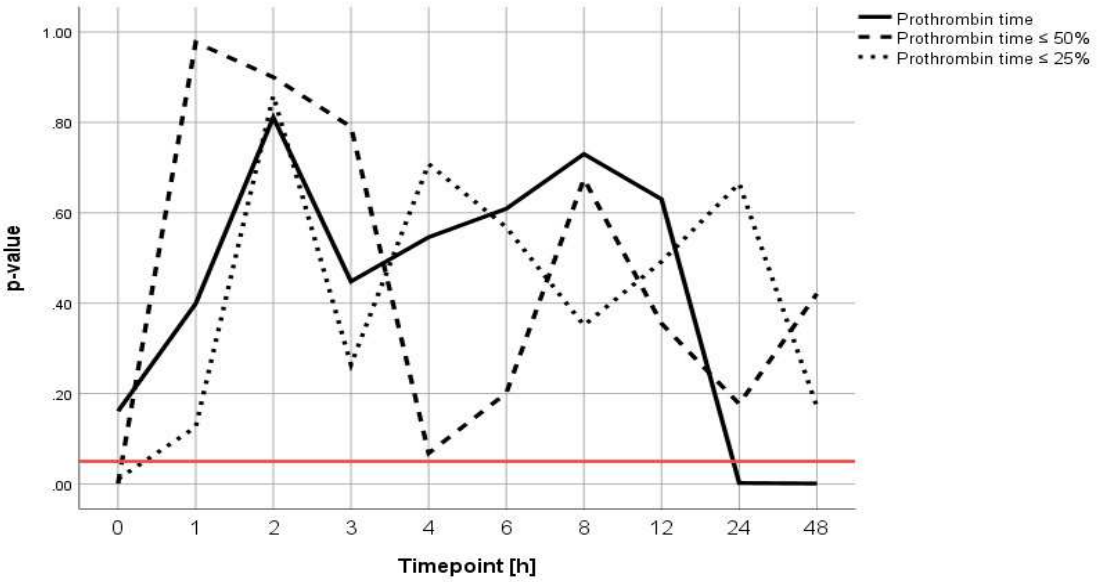

Figure 2: Prothrombin time as an independent predictor for sepsis, corrected for injury severity

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and later time course after polytrauma, making clinicians aware of its possible presence at these time points. However, the predictive ability of the parameter itself appears to only exist in the later course, as it was only significant at that point. This limitation highlights the association with injury severity, which showed an association with PT at admission. The finding confirms previous reports in stressing the necessity to reference PT to the latter [20,22-24].

Yet, PT cut-off values were independent predictors also early stages despite the correction for injury severity. This finding implies that absolute terms of PT should be considered, especially in cases a lower injury severity. The missing higher predictiveness of a more extreme PT threshold value (≤ 25%) is seen in the respectively low case number at each time point after admission (n < 20), which could be due to early mortality in these severe cases [20]. Considering the general course PT over the observational period of 48 h, a reduced hemostasis appears to occur independently of either group (septic/non-septic). This finding is interpreted in natural and iatrogenic causes, where increased or prolonged bleeding, acidosis, hypothermia [17], along with pharmaceutical (e.g., vasopressors, fluid resuscitation, substitution of hematologic components) or surgical measures may occur, respectively be performed, vastly affecting coagulation [25,26]. In general, the PT normalizes over time, which is congruent with the theory of SIRS and CARS (Compensatory Anti-inflammatory Response Syndrome) [10,11], where an early inflammatory response (SIRS) is followed by CARS. In this regard, coagulopathy should not be interepreted in the exclusive context of hemorrhage, but also in relation to the immunologic aspect, e.g., complement pathway activation [35]. The insights ought to enable clinicians a constant re-assessment to facilitate and refine immediate and preventive timely measures, which can be pharmaceutical or surgical. Specifically, the decision on surgical treatment extent, being damage-control or early total care [36], could be alleviated. Thereby, AE like sepsis (possibly resulting from a decompensating physiologic state) and subsequent mortality are intended to be minimized. Several limitations must be mentioned. The main aspect is the missing consideration of patient related variables. Especially the anticoagulant aspect must be respected at various time points: Patients, especially the senile age group, are commonly subject to anti-hemostatic medications during trauma. In the acute treatment phase (after admission), they are often treated (heavily) with fluids or hematologic components, altering metrics and function. In the further course, anticoagulation may have been initiated to prevent or treat thromboembolism in light of reduced or impaired mobility. Taking the long time frame of inclusion into account, treatment, especially the aforementioned factors, is subject to change as medical advances were achieved. It must also be noted that treatment according to current guidelines was continuously performed, which limits the room for flexible measures. The time frame for PT measurement was rather short at 48 h, because the measurements were restricted to intensive care units. Threshold values were defined, but should be interpreted cautiously, as sensitivity and specificity may not always be of equal importance. On the other hand, direct confounding by injury severity was limited by correction for the representing scores. Our results highlight the time-related role of PT for sepsis in polytrauma patients. Thereby re-assessment of reference values is enabled, and early appropriate measures are facilitated.

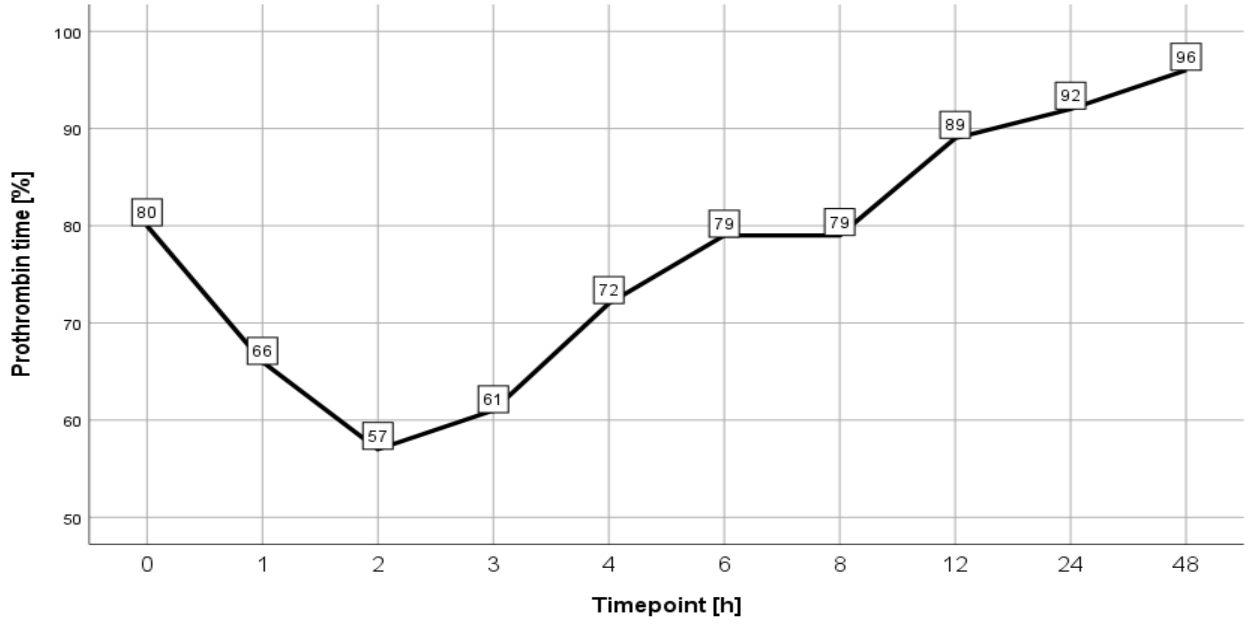

Figure 3: Time-related threshold values in prothrombin time between groups according to sepsis development.

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Conclusion

Significant differences in PT between groups existed from admission over an hour and from 24 h to 48 h after admission. PT reached a minimum at 2 h after admission (PT: 60%) and normalized thereafter. The PT represented an independent predictor of sepsis at 24 h (PT: 86%) and 48 h (PT: 91%) after admission. A PT of ≤ 50% was predictive at admission and tended to be predictive at 4 h after admission. A PT of ≤ 25% was predictive at admission. Threshold values reached a minimum at 2 h after admission (PT: 57%) and normalized thereafter. Our results highlight the time-related role of PT for sepsis in polytrauma patients. Thereby re-assessment is enabled, and early appropriate measures are facilitated.

Comment

Watson Trauma Pathway Explorer © by Ladislav Mica and IBM®.

Author contributions

P.V.: Data curation, Formal analysis, Investigation, Software, Visualization, Writing - original draft.

N.W.: Project administration, Software, Writing - review & editing.

J.H.: Data curation, Project administration, Software, Writing - review & editing.

C.N.: Data curation, Project administration, Software, Writing - review & editing.

J.V.: Project administration, Software, Writing - review & editing.

H.-C.P: Data curation, Project administration, Software, Writing - review & editing.

L.M.: Conceptualization, Data curation, Investigation, Methodology, Project administration,

Resources, Supervision, Validation, Writing - review & editing.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this paper. The authors declare no conflict of interest related to the submitted study.

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